

SYNTHESIS OF SOME HETEROCYCLIC RING SYSTEMS BASED ON PYRIDAZINE

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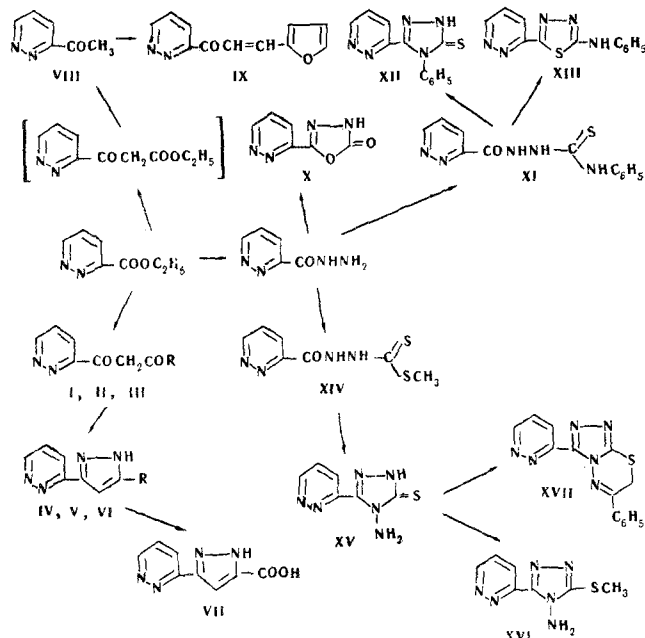
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Ethyl pyridazine-3-carboxylate is used to synthesize previously unknown pyridazine derivatives.

Continuing previous work [1, 2] on the synthesis of pyridazine-3-carboxylic acid systems, with a retarding influence on monoamineoxidase, the present paper deals with preparation of a number of other pyridazine derivatives containing another heterocyclic system along with pyridazine.

Thus the action of hydrazine on ω -acetyl, ω -propionyl, and ω -valeryl-3-acetopyridazine (I-III) gives 90-92% yields of 3-(3'-pyridazinyl)-5-alkylpyrazoles (IV-VI). The methyl group of 3-(3'-pyridazinyl)-5-methylpyrazole can be oxidized by aqueous potassium permanganate to carboxyl, but the total yield of 5-(3'-pyridazinyl)pyrazole-3-carboxylic acid (VII) is 18%. Pyridazine diketones I-III are prepared by ester condensation in the presence of sodium ethoxide, of ethyl pyridazine-3-carboxylate



with acetone, methylethyl ketone, and methylbutyl ketone respectively. The same method is used to synthesize ethyl pyridazinylacetate, decarboxylated by heating with 10% sulfuric acid, to 3-acetylpyridazine, (VIII) (IR $\nu_{\text{C=O}}$ 1704 cm^{-1}). The methyl group of VIII is readily condensed with aldehydes, e. g. furfural, to give the corresponding chalcone IX,

Treatment of the hydrazide of pyridazine-3-carboxylic acid with phosgene gives 5-(3'-pyridazinyl)-1,3,4-oxadizol-2-one (X).

3-(3'-pyridazinyl)-4-phenyl-1,2,4-triazole-2-thione (XII) and 3-(3'-pyridazinyl)-5-phenylamino-1,3,4-thiadiazole (XIII) are obtained by intramolecular condensations of 1-(3'-pyridazinyl)-4-phenylthiosemicarbazide (XI) in solution in sodium hydroxide and concentrated sulfuric acid. XI is prepared by heating an ethanol solution of the hydrazide of pyridazine-3-carboxylic acid with phenylisothiocyanate.

Reaction of the hydrazide of pyridazine-3-carboxylic acid with carbon disulfide in potassium hydroxide solution, followed by treatment with methyl iodide, gives methyl 2-(3'-pyridazinyl)dithiocarbazine (XIV). The latter is condensed with hydrazine to give 3-(3'-pyridazinyl)-4-amino-1,2,4-triazole-5-thione (XV). The structure of XV is confirmed by formation of a methylmercapto derivative XVI, and by reaction with ω -bromoacetophenone, to give 3-(3'-pyridazinyl)-5-phenyl-6,7-dihydro-7-thia-1,2,4,9-tetraazaindene (XVII).

None of the new pyridazine derivatives described has tuberculostatic activity.

EXPERIMENTAL

ω -Acetyl-3-acetopyridazine (I). 6.5 g (0.043 mole) Ethyl pyridazine-3-carboxylate, 3.0 g (0.044 mole) dry NaOEt, and 7 ml acetone, were mixed and kept at room temperature for 3 hr, then slightly warmed. The products were dissolved in 20 ml water, acidified with dilute HCl, neutralized with NaHCO_3 , and extracted with ether. After drying and distilling off the ether, the residue was recrystallized from heptane, using active charcoal. Yield 3 g (43%), pale-green crystals, mp 116°-117° C. Found: C 58.63; H 5.04; N 16.95%. Calculated for $\text{C}_8\text{H}_8\text{N}_2\text{O}_2$: C 58.53; H 4.91; N 17.07%.

In a similar way ethyl pyridazinyl-3-carboxylate, methylethyl ketone, and methyl butyl ketone, were used to prepare, respectively, ω -propionyl-3-acetopyridazine (II), [yield 2.5 g (33%), colorless crystals, acquiring a red reflex on keeping, mp 71°-72° C. Found: C 60.54; H 5.60; N 15.91%. Calculated for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_2$: C 60.66; H 5.66; N 15.72%], and ω -valeryl-3-acetopyridazine (III) [yield 2.0 g (23%), colorless flaky crystals, turning red on keeping, mp 53°-54° C. Found: C 64.24; H 6.91; N 13.50%. Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$: C 64.06; H 6.84; N 13.58%].

3-(3'-Pyridazinyl)-5-methylpyrazole (IV). 0.5 g (3 mM) I in 10 ml EtOH and 0.6 g hydrazine hydrate were refluxed together for 3 hr. Then the solvent was distilled off, and 2-3 ml water added to the resi-

due. The latter was then rubbed to make it crystallize, and the solid filtered off. Yield 0.45 g (92%), colorless crystals, mp 198°–199° C (ex EtOH).

Found: N 34.88%. Calculated for $C_9H_9N_4$: N 34.98%.

Similarly II and III gave 3-(3'-pyridazinyl)-5-ethylpyrazole (V) [yield 0.45 g (92%), colorless crystals, mp 118°–119° C (ex 25% EtOH). Found: N 32.18%. Calculated for $C_9H_{10}N_4$: N 32.16%] and 3-(3'-pyridazinyl)-5-butylpyrazole (VI) [yield 0.44 g (90%), colorless crystals, mp 110° C (ex 25% ethanol).

Found: N 27.63%. Calculated for $C_{11}H_{14}N_4$: N 27.70%].

5-(3'-Pyridazinyl)pyrazole-3-carboxylic acid (VII). A solution of 2 g $KMnO_4$ (13 mM) in 100 ml water was added to a solution of 1 g (6.2 mM) IV in 50 ml water which was heated on a water-bath, and CO_2 bubbled through it. The whole was then heated for 30 min longer, and if necessary excess $KMnO_4$ removed by adding a few drops of EtOH. The MnO_2 was filtered off, and the filtrate concentrated to 20–25 ml, brought to pH 4 with HCl, and then left to crystallize. Yield 0.2 g (18%) white precipitate of minute crystals, mp 295°–296° C (ex water). Found: C 50.25; H 3.28; N 29.32%. Calculated for $C_8H_6N_4O_2$: C 50.52; H 3.18; N 29.46%.

3-Acetylpyrazine (VIII). 6.5 g (0.043 mole) Ethyl pyridazine-3-carboxylate, 3.0 g (0.044 mole) dry NaOEt, and 5 ml EtOAc, were held for 3 hr at room temperature, then the mixture gently warmed. The products were dissolved in 10 ml water, acidified with dilute HCl, neutralized with $NaHCO_3$, and extracted with ether. The ether was distilled off, and the residue boiled with 45 ml 10% H_2SO_4 . After drying and distilling off the ether, the material was recrystallized from hexane, using decolorizing charcoal. Yield 1.6 g (28%) pale-yellow crystals, mp 87°–88° C. Found: C 52.30; H 4.45; N 20.14%. Calculated for $C_6H_6N_2O$: C 52.17; H 4.38; N 20.28%. 3-Acetylpyridazine dinitrophenylhydrazone mp 205°–206° C (ex EtOH). Found: N 27.54%. Calculated for $C_{12}H_{10}N_6O_4$: N 27.81%.

3-(Furfurylidenacetyl)pyridazine (IX). A solution of 0.5 g (1.2 mM) NaOH in 3 ml 10% EtOH was cooled to 0° C, 0.2 ml freshly-distilled furfural added, the mixture stirred vigorously with a glass rod, and 0.12 g (1 mM) VIII added. A bright-yellow precipitate immediately formed. The products were allowed to stand for 1 hr, filtered, and the solid washed with water. Yield 0.16 g (80%) IX, mp 104°–105° C (ex 25% EtOH). Found: C 66.28; H 4.28; N 13.88%. Calculated for $C_{11}H_8N_2O_2$: C 65.99; H 4.03; N 13.99%.

5-(3'-Pyridazinyl)-1,3,4-oxazolid-2-one (X). 20 ml Dioxane was saturated with phosgene, and a solution of 1.33 g (0.01 mole) pyridazine-3-carboxylic acid hydrazide in 30 ml dioxane added. A white precipitate formed. Phosgene was passed into the mixture for 1 hr, after which it was heated to boiling and filtered. Yield 1.3 g (79%) white crystals, mp 232°–233° C, (ex EtOH). Found: C 43.80; H 2.60; N 33.90%. Calculated for $C_6H_4N_4O_2$: C 43.91; H 2.45; N 34.14%.

1-(3'-Pyridazinoyl)-4-phenylthiosemicarbazide (XI). 0.3 g (0.022 mole) pyridazine-3-carboxylic acid

hydrazine and 0.3 g (0.022 mole) phenylisothiocyanate in 10 ml EtOH were heated to boiling, then cooled to 0° C, and the resultant precipitate filtered off and washed with 2 ml of each of EtOH and ether. Yield 0.52 g (83%) colorless crystals, mp 147°–148° C. Found: C 53.04; H 4.21; N 25.65; S 11.90%. Calculated for $C_{12}H_{11}N_5OS$: C 52.73; H 4.06; N 25.63; S 11.73%.

3-(3'-Pyridazinyl)-4-phenyl-1,2,4-triazole-5-thione (XII). 0.25 g (0.9 mM) XI was refluxed with 3 ml 2N NaOH for 15 min. After cooling the products were acidified with dilute HCl, and the precipitate filtered off and washed with water. Yield 0.11 g (47%) grayish crystals, mp 234°–235° C (ex EtOH). Found: C 56.36; H 3.74; N 27.28; S 12.74%. Calculated for $C_{12}H_9N_5S$: C 56.45; H 3.55; N 27.44; S 12.56%.

3-(3'-Pyridazinyl)-5-phenylamino-1,3,4-thiadiazole (XIII). 0.25 g (0.9 mM) XI was heated with 3 ml conc. H_2SO_4 on a steam-bath, and then left for 15 min. The products were mixed with 20 ml water, made alkaline with ammonia (pH 8) heated to boiling, cooled, the solid filtered off, and recrystallized ex 20 ml 75% EtOH. Yield 0.1 g (43%) colorless crystals, mp 253°–254° C. Found: C 56.31; H 3.89; N 27.14; S 12.56%. Calculated for $C_{12}H_9N_5S$: C 56.45; H 3.95; N 27.44; S 12.56%.

Methyl 2-(3'-pyridazinyl)dithiocarbazine (XIV). 1.38 g (0.01 mole) Pyridazine-3-carboxylic acid hydrazide and 0.65 g (0.012 mole) KOH were dissolved with gentle warning in 15 ml dry EtOH, 3 ml CS_2 added, the mixture shaken vigorously, and left for 2–3 hr with occasional shaking and rubbing of the precipitate. 30 ml ether was then added, and the solid filtered off, dissolved in 30 ml water, 2 ml MeI added, and the mixture shaken a few times in a mechanical shaker. The initial viscous mass gradually crystallized. The solid was filtered off and washed with water to give 1.8 g (80%) yellowish crystals, mp 174°–175° C (ex dry EtOH). Found: C 36.71; H 3.50; N 24.55; S 28.15%. Calculated for $C_7H_8N_4OS_2$: C 36.82; H 3.53; N 24.54; S 28.09%.

3-(3'-Pyridazinyl)-4-amino-1,2,4-triazole-5-thione (XV). 2 g (8.8 mM) XIV was heated with 15 ml EtOH to dissolve it, 2 ml 50% hydrazine hydrate added, and the whole boiled for 2 hr. The alcohol was distilled off, the residue dissolved in 20 ml water, acidified with dilute HCl, the solid filtered off, and recrystallized from EtOH. Yield 1.03 g (60%), colorless crystals, mp 163°–164° C. Found: C 37.25; H 3.21; N 43.20; S 16.64%. Calculated for $C_6H_6N_6S$: C 37.10; H 3.11; N 43.28; S 16.51%.

3-(3'-Pyridazinyl)-4-amino-5-methylmercapto-1,2,4-triazole (XVI). 0.8 g (4 mM) XV and 8 ml 1 N NaOH were mixed with 0.8 ml MeI and 1 ml MeOH. The whole was stirred and rubbed for 30 min, the solid filtered off, and recrystallized from 50 ml EtOAc. Yield 0.5 g (59%) colorless crystals, mp 149°–150° C. Found: C 39.52; H 3.99; N 40.15; S 15.17%. Calculated for $C_7H_8N_6S$: C 40.39; H 3.84; N 40.35; S 15.40%.

3-(3'-Pyridazinyl)-5-phenyl-6,7-dihydro-7-thia-1,2,4,9-tetraazindene (XVII). 0.1 g (0.05 mM) X and

0.1 g (0.05 mM) ω -bromoacetophenone in 3 ml dry EtOH were refluxed for 2 hr, the products cooled, and the solid filtered off, yield 0.14 g (93%), pale-rose colored crystals, mp 209°–210° C (ex EtOH). Found: C 57.43; H 3.55; N 28.50; S 10.84%. Calculated for $C_{14}H_{10}N_6S$: C 57.13; H 3.42; N 28.56; S 10.89%.

2. G. P. Sokolov and S. A. Hiller, Author's certificate 134269, 1959.

REFERENCES

1. S. A. Hiller, E. Ya. Baumanis, G. P. Sokolov, and V. Ya. Grinshtein, DAN, 145, 440, 1962.

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